

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 13 August 1999 (13.08.99)	
<b>International application No.</b> PCT/JP99/00175	<b>Applicant's or agent's file reference</b> 2501WO0P
<b>International filing date (day/month/year)</b> 20 January 1999 (20.01.99)	<b>Priority date (day/month/year)</b> 21 January 1998 (21.01.98)
<b>Applicant</b> SHIMIZU, Hisayoshi et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

24 June 1999 (24.06.99)



in a notice effecting later election filed with the International Bureau on:

2. The election
- ☒
- was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  Sean Taylor  Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>2501W00P</b>	<b>FOR FURTHER ACTION</b>		see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. <b>PCT/JP 99/ 00175</b>	International filing date (day/month/year) <b>20/01/1999</b>	(Earliest) Priority Date (day/month/year) <b>21/01/1998</b>	
Applicant  <b>TAKEDA CHEMICAL INDUSTRIES, LTD. et al.</b>			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

**4. With regard to the title,**

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**LYOPHILIZATION METHOD FOR SUSTAINED-RELEASE PREPARATIONS**

**5. With regard to the abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/ 00175

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: —  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds described by the expression "water-repelling base material" in claim 1, the search has been restricted to the compounds cited in the description (page 3, lines 16-23) and claim 6, for economic reasons (PCT Search Guidelines PCT/GL/2 Chapter III, 2.1, 3.6 and 3.7).

# PATENT COOPERATION TREATY

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

## PCT

To:

KELLER, Günter  
LEDERER, KELLER & RIEDERER  
Prinzregentenstr. 16  
D - 80538 München  
ALLEMAGNE

LEDERER, KELLER & RIEDERER

EINGANG / RECEIPT

30. NOV. 1999

WRITTEN OPINION

(PCT Rule 66)

29. Feb. 00 4

Date of mailing  
(day/month/year)

29. 11. 99

Applicant's or agent's file reference

2501WO0P

REPLY DUE

within 3 month(s)  
from the above date of mailing

International application No.

PCT/JP99/00175

International filing date (day/month/year)

20/01/1999

Priority date (day/month/year)

21/01/1998

International Patent Classification (IPC) or both national classification and IPC

A61K9/19

Applicant

TAKEDA CHEMICAL INDUSTRIES, LTD. et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 21/05/2000.

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Georgopoulos, N

Formalities officer (incl. extension of time limits)

Tantum, P

Telephone No. +49 89 2399 2651



## WRITTEN OPINION

International application No. PCT/JP99/00175

### I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

#### Description, pages:

1-38 as originally filed

#### Claims, No.:

1-8 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

### V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### 1. Statement

Novelty (N)	Claims 1, 3-8
Inventive step (IS)	Claims 1-8
Industrial applicability (IA)	Claims

#### 2. Citations and explanations

see separate sheet

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

Item V

- 1 Reference is made to the following documents:

D1: EP-A-0 394 050

D2: G D J ADAMS: "Freeze-drying of biological materials" DRYING TECHNOLOGY, vol. 36, no. 9, 1 January 1991, pp.891-925 XP002078741

- 2 The present application does not fulfil the requirements of Article 33 (2) PCT because the subject-matter of independent claim 1 (method) as well as that of dependent claims 3 to 8 as far as they refer to claim 1 is not new. On the contrary, the subject-matter of independent claim 2 (method) is new.

2.1 In particular,

D1 discloses a method of preparing a freeze-dried preparation in which a first liquid is frozen, a second liquid is added to the frozen first liquid and is frozen thereon, and the frozen first and second liquids are freeze-dried together, in which at least one of said first and second liquids contains a pharmaceutical compound or preparation dissolved or suspended therein (see claim 1 of D1). In example 5 of D1, the inner face of a vial is covered with an ice layer, then with a second layer containing pharmaceutical compounds and, finally, said vial is transferred into a freeze-dryer, which is disclosed in present claim 1.

D1 does, however, not disclose the step of partially or wholly coating the inner face of a freeze-drying container with a water-repelling base material as claimed in present claim 2.

D2 discloses a freeze-drying method in which foodstuffs, chemicals and bulk pharmaceuticals may be dispensed into teflon coated trays (see page 905, paragraphs 2 and 3 of D2). D2 does not mention the step of further partially or wholly coating the coated inner face of a freeze-drying container with an ice layer, as claimed in present claim 2.

- 2.2 Therefore, the subject-matter of independent claim 1 (method) is anticipated by the technical teaching of any of the documents D1 or D2. Unlike present claim 1, the



subject-matter of independent claim 2 (method) is not anticipated by the technical teaching of any of the documents D1 or D2.

- 3 The present application does not fulfil the requirements as set forth in Article 33 (3) PCT because the subject-matter of independent claim 2 (method) does not involve an inventive step, for the following reasons:
- 3.1 The closest prior art document is considered to be represented by document D1. The technical problem to be solved by the present invention may, therefore, be regarded as how to provide an alternative method to that of D1, which:
- i/ reduces the risk of the resulting microspheres being contaminated from microorganisms,
  - ii/ eliminates the risk of production and entry of foreign substances into said microspheres, and
  - iii/ exhibits high and more constant microsphere recovery rate as well as higher microsphere recovery yield (see page 24, line 35 to page 25, line 14 of the present description as well as page 11, lines 3 to 12 of D1). The difference between the method of the present invention and that of D1 resides in the step of partially or wholly coating the inner face of a freeze-drying container with a water-repelling base material. Said difference seems to be a trivial design possibility, not related to any unexpected effect or advantage (see page 2, lines 19 to 23 of the present description). Thus, the method of present claim 2 would be obvious to the person skilled in the art having regard to D1.
- 4 The subject-matter of claims 1 to 8 is susceptible of industrial application in the field of pharmaceuticals industry (Article 33 (4) PCT).

**Item VII**

- 5 Contrary to the requirements of Rule 5.1 (a) (ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

**Item VIII**

**WRITTEN OPINION  
SEPARATE SHEET**

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International application No. PCT/JP99/00175

- 6 The expressions "solid sustained-release preparation" and "freeze-drying container" in claims 1 and 2 are not fully supported by the description (Article 6 PCT and PCT-Guidelines, C-III, 6.5).
- 7 The word "recoverd" on page 25, lines 13 and 14 as well as the expression "more high" on page 25, line 14 of the present description should read "recovered" and "higher", respectively.
- 8 The applicant is requested to file amendments by way of replacement pages in the manner stipulated by Rule 66.8 (a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate. Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8 (a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2501WO0P		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP99/00175	International filing date (day/month/year) 20/01/1999	Priority date (day/month/year) 21/01/1998
International Patent Classification (IPC) or national classification and IPC A61K9/19		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 24/06/1999	Date of completion of this report 05.04.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Georgopoulos, N Telephone No. +49 89 2399 2634 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP99/00175

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-38 as originally filed

**Claims, No.:**

1-8 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 2
	No:	Claims 1, 3-8
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-8
Industrial applicability (IA)	Yes:	Claims 1-8
	No:	Claims

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP99/00175

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2. Citations and explanations

see separate sheet

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

see separate sheet

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Item V

- 1 Reference is made to the following documents:

D1: EP-A-0 394 050

D2: G D J ADAMS: "Freeze-drying of biological materials" DRYING TECHNOLOGY, vol. 36, no. 9, 1 January 1991, pp.891-925 XP002078741

- 2 The present application does not fulfil the requirements of Article 33 (2) PCT because the subject-matter of independent claim 1 (method) as well as that of dependent claims 3 to 8 as far as they refer to claim 1 is not new. On the contrary, the subject-matter of independent claim 2 (method) is new.

- 2.1 D1 discloses a method of preparing a freeze-dried preparation in which a first liquid is frozen, a second liquid is added to the frozen first liquid and is frozen thereon, and the frozen first and second liquids are freeze-dried together, in which at least one of said first and second liquids contains a pharmaceutical compound or preparation dissolved or suspended therein (see claim 1 of D1). In example 5 of D1, the inner face of a vial is covered with an ice layer, then with a second layer containing pharmaceutical compounds and, finally, said vial is transferred into a freeze-dryer, which is disclosed in present claim 1.

D1 does, however, not disclose the step of partially or wholly coating the inner face of a freeze-drying container with a water-repelling base material as claimed in present claim 2.

D2 discloses a freeze-drying method in which foodstuffs, chemicals and bulk pharmaceuticals may be dispensed into teflon coated trays (see page 905, paragraphs 2 and 3 of D2). D2 does not mention the step of further partially or wholly coating the coated inner face of a freeze-drying container with an ice layer, as claimed in present claim 2.

- 2.2 Therefore, the subject-matter of independent claim 1 (method) is anticipated by the technical teaching of any of the documents D1 or D2. Unlike present claim 1, the subject-matter of independent claim 2 (method) is not anticipated by the technical teaching of any of the documents D1 or D2.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/JP99/00175

- 3 The present application does not fulfil the requirements as set forth in Article 33 (3) PCT because the subject-matter of independent claim 2 (method) does not involve an inventive step, for the following reasons:
- 3.1 The closest prior art document is considered to be represented by document D1. The technical problem to be solved by the present invention may, therefore, be regarded as how to provide an alternative method to that of D1, which:
- i/ reduces the risk of the resulting microspheres being contaminated from microorganisms,
  - ii/ eliminates the risk of production and entry of foreign substances into said microspheres, and
  - iii/ exhibits high and more constant microsphere recovery rate as well as higher microsphere recovery yield (see page 24, line 35 to page 25, line 14 of the present description as well as page 11, lines 3 to 12 of D1). The difference between the method of the present invention and that of D1 resides in the step of partially or wholly coating the inner face of a freeze-drying container with a water-repelling base material. Said difference seems to be a trivial design possibility, not related to any unexpected effect or advantage (see page 2, lines 19 to 23 of the present description). Thus, the method of present claim 2 would be obvious to the person skilled in the art having regard to D1.
- 4 The subject-matter of claims 1 to 8 is susceptible of industrial application in the field of pharmaceuticals industry (Article 33 (4) PCT).

**Item VII**

- 5 Contrary to the requirements of Rule 5.1 (a) (ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.
- 6 The word "recoverd" on page 25, lines 13 and 14 as well as the expression "more high" on page 25, line 14 of the present description should read "recovered" and "higher", respectively (Rule 91 (1) (b) PCT).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/JP99/00175

**Item VIII**

- 7 The expressions "solid sustained-release preparation" and "freeze-drying container" in claims 1 and 2 are not fully supported by the description (Article 6 PCT and PCT-Guidelines, C-III, 6.5).



# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>2501WOOP</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/JP 99/ 00175</b>	International filing date (day/month/year) <b>20/01/1999</b>	(Earliest) Priority Date (day/month/year) <b>21/01/1998</b>
Applicant <b>TAKEDA CHEMICAL INDUSTRIES, LTD. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

### 4. With regard to the title,

- ☐ the text is approved as submitted by the applicant.
- ☒ the text has been established by this Authority to read as follows:

**LYOPHILIZATION METHOD FOR SUSTAINED-RELEASE PREPARATIONS**

### 5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

### 6. The figure of the drawings to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/00175

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds described by the expression "water-repelling base material" in claim 1, the search has been restricted to the compounds cited in the description (page 3, lines 16-23) and claim 6, for economic reasons (PCT Search Guidelines PCT/GL/2 Chapter III, 2.1, 3.6 and 3.7).

## INTERNATIONAL SEARCH REPORT

National Application No

PCT/JP 99/00175

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K9/19 F26B5/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K F26B A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 394 050 A (SANKYO CO) 24 October 1990 see page 3, line 33-42 see page 4, line 11-26 see page 4, line 34-42 see page 4, line 51-52 see example 5 see claims 1-3, 9-13, 17 ----	1,3-5,8 2,7
X	G D J ADAMS: "Freeze-drying of biological materials" DRYING TECHNOLOGY, vol. 36, no. 9, 1 January 1991, page 891 925 XP002078741	1,4,6
Y	see page 905, line 3-7 ----- -/--	2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 May 1999

Date of mailing of the international search report

04/06/1999

Name and mailing address of the ISA  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

La Gaetana, R

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 99/00175

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 781 548 A (TAKEDA CHEMICAL INDUSTRIES LTD) 2 July 1997	7
A	cited in the application see page 2, line 23-35 see page 8, line 33-47 see examples see claims -----	1-6, 8

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 99/00175

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0394050 A	24-10-1990	AU 624494 B	11-06-1992
		AU 5328990 A	25-10-1990
		CA 2014714 A	18-10-1990
		JP 3047115 A	28-02-1991
		JP 7116022 B	13-12-1995
		KR 9507908 B	21-07-1995
		NO 180801 B	24-03-1997
		US 5044091 A	03-09-1991
EP 0781548 A	02-07-1997	CA 2192773 A	16-06-1997
		JP 9221417 A	26-08-1997

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2501WO0P	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP99/00175	International filing date (day/month/year) 20/01/1999	Priority date (day/month/year) 21/01/1998
International Patent Classification (IPC) or national classification and IPC A61K9/19		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  24/06/1999	Date of completion of this report  05.04.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Georgopoulos, N  Telephone No. +49 89 2399 2634 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP99/00175

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-38 as originally filed

**Claims, No.:**

1-8 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 2
	No:	Claims 1, 3-8
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-8
Industrial applicability (IA)	Yes:	Claims 1-8
	No:	Claims



**INTERNATIONAL PRELIMINARY  
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2. Citations and explanations

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Item V**

- 1 Reference is made to the following documents:  
D1: EP-A-0 394 050  
D2: G D J ADAMS: "Freeze-drying of biological materials" DRYING TECHNOLOGY, vol. 36, no. 9, 1 January 1991, pp.891-925 XP002078741
- 2 The present application does not fulfil the requirements of Article 33 (2) PCT because the subject-matter of independent claim 1 (method) as well as that of dependent claims 3 to 8 as far as they refer to claim 1 is not new. On the contrary, the subject-matter of independent claim 2 (method) is new.
  - 2.1 D1 discloses a method of preparing a freeze-dried preparation in which a first liquid is frozen, a second liquid is added to the frozen first liquid and is frozen thereon, and the frozen first and second liquids are freeze-dried together, in which at least one of said first and second liquids contains a pharmaceutical compound or preparation dissolved or suspended therein (see claim 1 of D1). In example 5 of D1, the inner face of a vial is covered with an ice layer, then with a second layer containing pharmaceutical compounds and, finally, said vial is transferred into a freeze-dryer, which is disclosed in present claim 1.  
D1 does, however, not disclose the step of partially or wholly coating the inner face of a freeze-drying container with a water-repelling base material as claimed in present claim 2.  
  
D2 discloses a freeze-drying method in which foodstuffs, chemicals and bulk pharmaceuticals may be dispensed into teflon coated trays (see page 905, paragraphs 2 and 3 of D2). D2 does not mention the step of further partially or wholly coating the coated inner face of a freeze-drying container with an ice layer, as claimed in present claim 2.
  - 2.2 Therefore, the subject-matter of independent claim 1 (method) is anticipated by the technical teaching of any of the documents D1 or D2. Unlike present claim 1, the subject-matter of independent claim 2 (method) is not anticipated by the technical teaching of any of the documents D1 or D2.

- 3 The present application does not fulfil the requirements as set forth in Article 33 (3) PCT because the subject-matter of independent claim 2 (method) does not involve an inventive step, for the following reasons:
- 3.1 The closest prior art document is considered to be represented by document D1. The technical problem to be solved by the present invention may, therefore, be regarded as how to provide an alternative method to that of D1, which:
- i/ reduces the risk of the resulting microspheres being contaminated from microorganisms,
  - ii/ eliminates the risk of production and entry of foreign substances into said microspheres, and
  - iii/ exhibits high and more constant microsphere recovery rate as well as higher microsphere recovery yield (see page 24, line 35 to page 25, line 14 of the present description as well as page 11, lines 3 to 12 of D1). The difference between the method of the present invention and that of D1 resides in the step of partially or wholly coating the inner face of a freeze-drying container with a water-repelling base material. Said difference seems to be a trivial design possibility, not related to any unexpected effect or advantage (see page 2, lines 19 to 23 of the present description). Thus, the method of present claim 2 would be obvious to the person skilled in the art having regard to D1.
- 4 The subject-matter of claims 1 to 8 is susceptible of industrial application in the field of pharmaceuticals industry (Article 33 (4) PCT).

**Item VII**

- 5 Contrary to the requirements of Rule 5.1 (a) (ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.
- 6 The word "recoverd" on page 25, lines 13 and 14 as well as the expression "more high" on page 25, line 14 of the present description should read "recovered" and "higher", respectively (Rule 91 (1) (b) PCT).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/JP99/00175

**Item VIII**

- 7 The expressions "solid sustained-release preparation" and "freeze-drying container" in claims 1 and 2 are not fully supported by the description (Article 6 PCT and PCT-Guidelines, C-III, 6.5).